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CHEMICAL RESEARCH, DEVELOPMENT & ENGINEERING CENTER

CRDEC-TR-357

COMPUTER-ASSISTED DETERMINATION OF MINIMUM ENERGY CONFORMATIONS

V. BIS-1-METHYLPYRIDINIUM COMPOUNDS CONTAINING 1,4-DIACETYLBENZENE LINKAGE BETWEEN THE PYRIDINE MOIETIES: RELATIONSHIPS WITH ACETYLCHOLINESTERASE ACTIVITY

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13. ABSTRACT (Maximum 200 words)

To achieve optimized geometries using the empirical Molecular Mechanics II computer program, conformational analyses were performed on three-dimensional representations of selected bispyridinium compounds having 1,4-diacetylbenzene linkage between the pyridine moieties. Three-dimensional atom cartesian coordinates for the minimum energy conformations of the compounds are reported.

Optimized geometries were also calculated for pyridostigmine, hexamethonium, octamethonium, and decamethonium. The resultant geometries were used to develop structure-activity relationships for AChE inhibition. The bispyridinium compounds' AChE inhibition is related to the interatomic distance between the bisquaternary nitrogens and/or the distance between specified atoms within an individual structure.

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PREFACE

The work described in this report was authorized under Project No. 1C162622A554, Chemical Munitions. This work was started in June 1988 and completed in May 1991.

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CONTENTS

LIST OF FIGURES AND TABLES

COMPUTER-ASSISTED DETERMINATION OF MINIMUM ENERGY CONFORMATIONS V. BIS-1-METHYLPYRIDINIUM COMPOUNDS CONTAINING 1,4-DIACETYLBENZENE LINKAGE BETWEEN THE PYRIDINE MOIETIES: RELATIONSHIPS WITH ACETYLCHOLINESTERASE ACTIVITY

1. INTRODUCTION

Compounds that interact with acetylcholinesterase (AChE) display inhibitory action due to the physicochemical, geometric, and electronic characteristics of their molecular structure. Previous structure activity studies[1-11] have identified important parameters/descriptors, geometric (interatomic distances) and functional groups [charged nitrogen or charged bisquaternary nitrogens; aromatic ring; oxygen (phosphoryl, carbonyl, hydroxyl)] that relate to resultant AChE activity.

Information from these studies have identified that compounds can interact with AChE at two anionic sites: an active/catalytic site and a peripheral/regulatory site.[1,4,6] Structure-activity studies have provided models, which relate structural features to AChE inhibition and the degree of inhibition.[1-11]

Hsu[12,*] reports on the synthesis and AChE inhibition of a new series of bis-1-methylpyridinium compounds (Figure 1) designed to incorporate structural features similar to compounds known to interact with AChE. To identify structure-AChE inhibition relationships of this series, a computer assisted theoretical computational analysis was performed. Previous studies[13-15] discuss the theoretical perspective, the general methodology, and the Molecular Modeling, Analysis and Display System (MMADS) that our group has used to optimize chemical structures and define their minimum energy conformation or shape. In this study, the same methodology was used.

The results of the computational analysis for the new bis-1-methylpyridinium compounds are reported.

2. EXPERIMENTATION

2.1 Compound Structures.

Eight compounds (Table 1) were analyzed. These are the three bispyridinium compounds synthesized for evaluation (Figure 1); and compounds known to interact at AChE that have structural features from which the bispyridinium compounds were designed (Figure 2).

*Hsu, F.-L., Ray, R., Clark, O.E., Munavalli, S., and Ashman, W.P., Synthesis and Anticholinesterase Activity of New Bispyridinium Compounds, undated, unpublished data.

Table 1. Compounds Analyzed

Name	Chemical Name	Common Name
Compound 1	1,4-Diacetylbenzene-α,α'-bis[2-(1-methylpyridinium)]	
Compound 2	1,4-Diacetylbenzene-α,α'-bis[3-(1-methylpyridinium)]	
Compound 3	1,4-Diacetylbenzene-α,α'-bis[4-(1-methylpyridinium)]	
Compound 4	1-4,4'-Bis(acetophenone)-α,α'-bispyridinium	
Compound 5	3-{[(Dimethylamino)-carbonyl]oxy)-1-methylpyridinium	Pyridostigmine
Compound 6	decamethylenebis[trimethylammonium]	Decamethonium
Compound 7	octamethylenebis[trimethylammonium]	Octamethonium
Compound 8	hexamethylenebis[trimethylammonium]	Hexamethonium

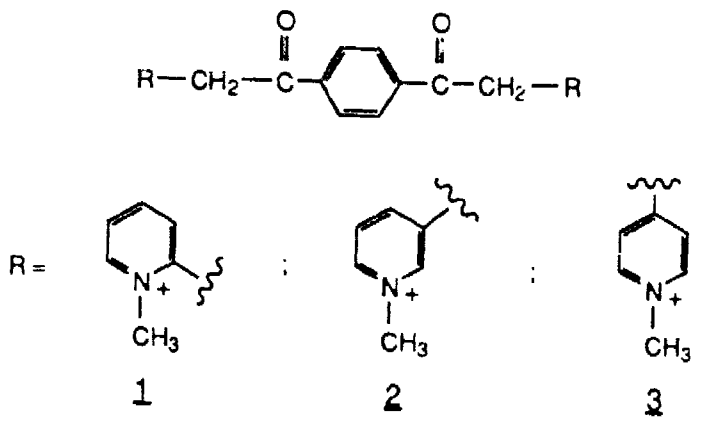
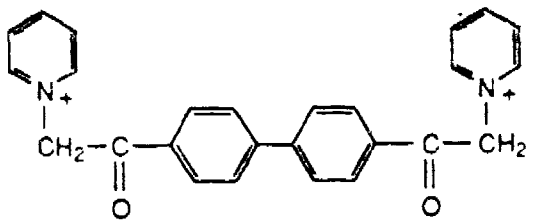


Figure 1. Chemical Structures of Bispyridinium Compounds



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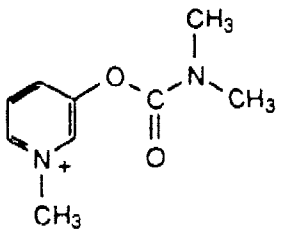

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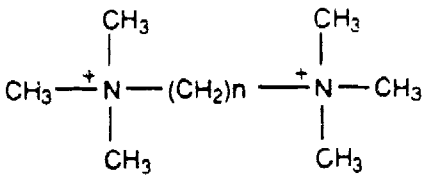

6, n = 10 7, n = 8 8, n = 6

Figure 2. Chemical Structures of Compounds 4-8

2.2 Three-Dimensional Minimum Energy Conformation Optimization.

Conformational minimum energy calculations were performed to achieve molecular mechanics structure optimization[16] (optimized geometries) using the empirical MM2 (QCPE version dated 1980) computer program developed by Allinger and Yuh.[17] The Chemometric and Biometric Modeling Branch, Research Directorate, U.S. Army Chemical Research, Development and Engineering Center MMADS (version 3.1) was used to incorporate the structures and perform the minimum energy calculations.

Every effort was made to locate the global minimum energy conformation for the compounds studied. However, because bispyridinium compounds can be polymorphic (can exist in more than one conformation under similar physicochemical environments),[18] the computational analysis included all conformers within 0.7 kcal energy difference. Figure 3 illustrates the possible syn- and anti-polymorphs for Compounds 1-3.

Initial starting conformations were constructed by orienting atoms and rings in various combinations of syn- and anticonformations. Dihedral angles for rings and substituent atom chains were rotated every 30°. For each 30° increment, energy minimizations were performed to differentiate between local minima. After finding the local minima, the substituent groups and rings were then rotated at smaller degree increments until the minimum energy conformation was obtained.

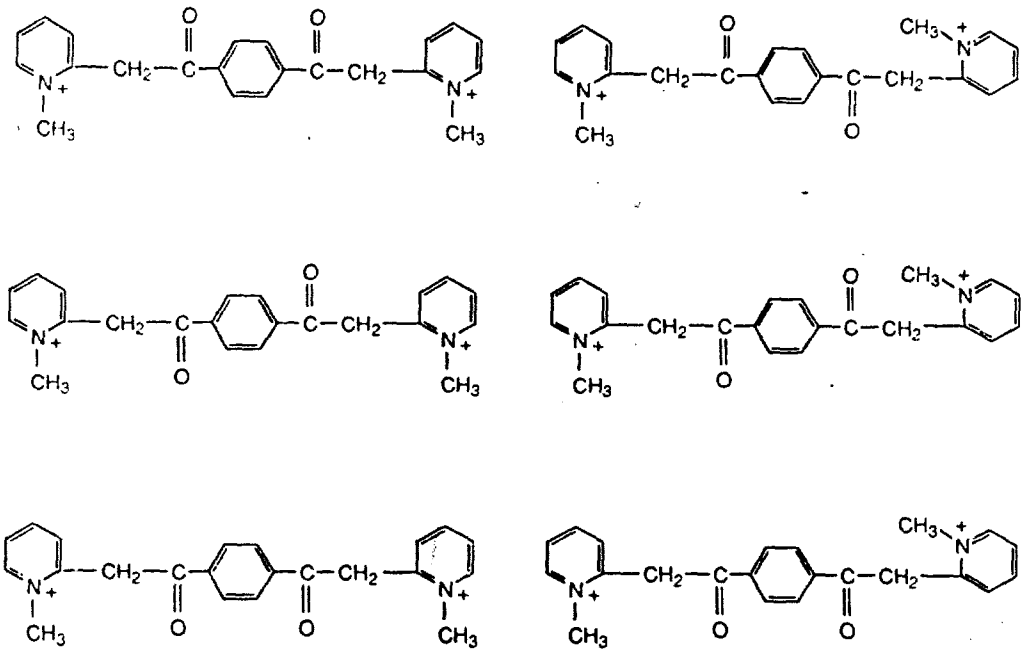

Figure 3. Various Conformations of Compound 1

Computer-assisted determinations of the minimum energy conformations were executed on a Digital Equipment Corporation (DEC) MicroVax II within a VMS operating system environment. A Tektronix 4105 series color graphics computer terminal was used to manipulate the structures and perform molecular modeling.

Interatomic distances between specific atoms were calculated using MMADS. Figure 4 illustrates the distances measured. The distances are measured between each pyridinium nitrogen and (1) the adjacent carbonyl carbon (a,a'); (2) the carbonyl oxygen (b,b'); and (3) the bisquaternary nitrogens (c) of each bisquaternary structure. Calculations were also made for compounds 4-8.

2.3 Anticholinesterase Activity.

The anti-AChE activities of the compounds 1-5 were determined calorimetrically using purified electric eel AChE.* The relative anti-AChE potencies were determined by studying enzyme inhibition at different concentrations of the compounds to obtain the IC50 values (molar concentration required to inhibit 50% eel AChE in vitro).

*Hsu, F.-L., Ray, R., Clark, O.E., Munavalli, S., and Ashman, W.P., Synthesis and Anticholinesterase Activity of New Bis-pyridinium Compounds, undated, unpublished data.

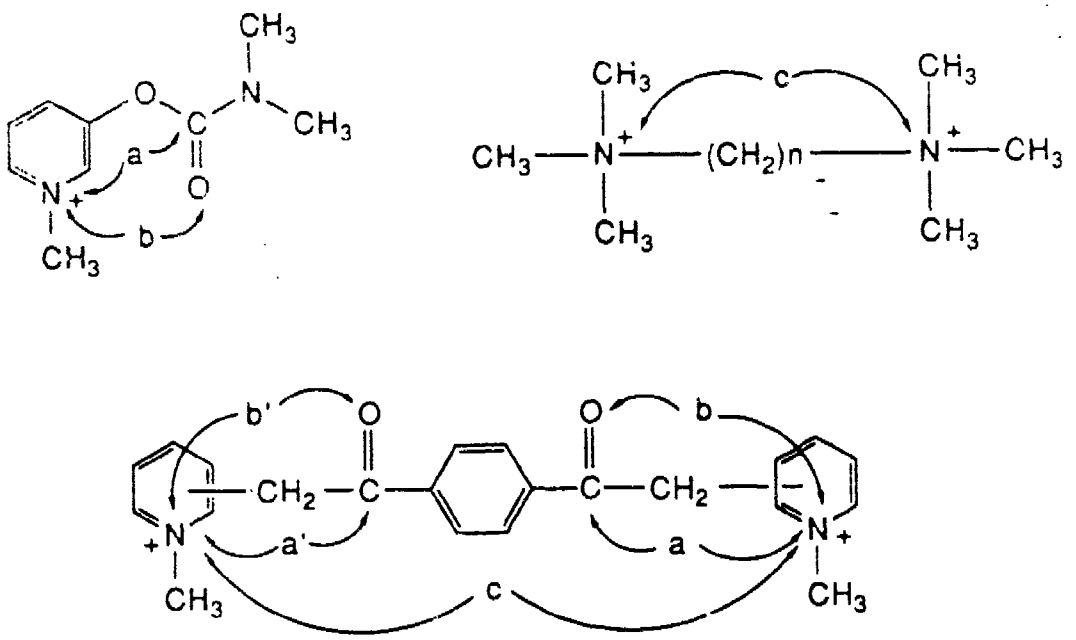

Figure 4. Interatomic Distances of Compounds 1-3 and 5-8

3. RESULTS

3.1 Conformational Analysis.

Compounds 1-4 and pyridostigmine[5] had various conformations that had local energy minima within 0.7 kcal of the lowest minimum energy conformation calculated. Because of this small energy difference, it is reasonable to predict that these conformations could occur in each compound. In compounds 1 and 2, the conformational changes are due to the potential for (1) the pyridinium rings of each structure, therefore, the ring nitrogens to be rotated in relation to the carbonyl oxygen, and (2) the pyridinium rings of the molecule to be rotated around an axis formed by the phenyl ring, carbonyl and methylene groups of the structure so that the rings may be syn and anti to each other along this axis. Compounds 3 and 4 have anti-substituents in positions 4 and 1 of the pyridinium ring, respectively: therefore, the number of possible polymorphs is reduced.

Table 2 gives the calculated interatomic distances for compounds 1-4 between each pyridinium nitrogen and the adjacent carbonyl carbon (distances a,a') and the carbonyl oxygen (distances b,b'); and between the nitrogens (distance c) of each bispyridinium structure. Conformational analysis calculations were also made for the compounds known to have anti-AChE

Table 2. Interatomic Distances and Relative Anti-AChE Potencies of Bisquaternary and Selected Ammonium Compounds

Compound	Distance Between Atoms in Å					IC50(M)*
	a	b	a'	b'	c	
2	4.31	4.77	4.32	4.80	8.82	4.0×10^{-8}
	4.31	4.77	4.74	5.64	9.30	
	4.27	4.91	4.77	5.67	10.83	
	4.33	4.80	4.92	5.74	11.78	
	4.72	5.62	4.74	5.63	9.28	
	4.74	5.64	4.92	5.74	12.02	
	4.49	4.23	4.73	5.62	11.29	
1	3.14	3.86	3.14	3.86	7.83	3.0×10^{-6}
	3.16	3.85	3.15	3.87	8.02	
	3.14	3.86	3.86	4.70	9.17	
	3.13	3.79	3.84	4.73	9.75	
	3.82	4.73	3.86	4.70	10.43	
	3.81	4.72	3.84	4.71	10.59	
3	5.03	5.69	5.04	5.81	9.86	3.0×10^{-5}
	5.11	5.84	5.04	5.71	12.43	
4	2.36	3.05	2.38	3.12	12.13	1.3×10^{-7}
	2.39	3.14	2.41	3.17	12.56	
Pyridostigmine	4.34	4.82	-	-	-	5.0×10^{-7}
	4.34	4.50	-	-	-	
	4.36	5.13	-	-	-	
	4.34	5.00	-	-	-	
Decamethonium	-	-	-	-	14.09	
Octamethonium	-	-	-	-	11.53	
Hexamethonium	-	-	-	-	8.99	

activity, pyridostigmine, a monoquaternary pyridinium compound that acts at the catalytic AChE site, and the bisquaternary compounds (i.e., decamethonium) that can act at the peripheral anionic site.

3.2 Structure-Activity Relationships.

The importance of the substituent's of compounds 1-4 on the pyridinium moiety for anti-AChE activity follows trends for other compounds known to interact at AChE. For instance, the 3-substituted isomer, 2, is the most active compound and the 2-substituted isomer, 1, was about one hundredth as active as 2, and the 4-substituted isomer, 3, was the least active. In inhibiting AChE, there are two anionic regions (catalytic site and peripheral site) that can be involved. In the catalytic region of AChE, there exists an anionic binding region and an esteratic site separated at a distance of approximately 5.0 Å.[1,5,7,10] Therefore, a compound interacting at this catalytic site would display optimal inhibition of its N+-C=0 and N+-carbonyl oxygen interatomic distance corresponded to that of the AChE site. Foldes[10] has corroborated this assumption and has reported on monoquaternary compounds that, as the compounds' N+-C=0 distance varies from 4.7 ± 0.8 Å, the IC50 values increase (the anti-AChE activity decreases). Pyridostigmine, a meta-substituted N,N-dimethyl carbamoyl pyridinium and an active AChE inhibitor, has calculated N+-C=0 distances (Table 2) for its various conformations from 4.34 to 4.36 Å and N+-carbonyl oxygen distances from 4.5 to 5.74 Å. Compound 2, the most active bisquaternary molecule of this study, has interatomic distances (Table 2) for its conformers of 4.31 to 4.91 Å for N+-C=0 and 4.23 to 5.74 Å for N+-carbonyl oxygen. The corresponding IC50 values are similar.

Compound 1 has N+-C=0 distances that vary from 3.13 to 3.86 Å, and N+-carbonyl distances that vary from 4.23 to 4.73 Å. The corresponding interatomic distances for 3 are 5.03 to 5.11 Å and 5.69 to 5.84 Å. The IC50 values are increased (less active) for these compounds.

Compound 4 has N+-C=0 distances of 2.36 to 2.41 Å and N+-carbonyl oxygen distances of 3.05 to 3.17 Å. Its IC50 value is similar to that of pyridostigmine. This is not in agreement if compound 4 acts at the catalytic AChE site. However, bisquaternary compounds are known to act at the peripheral anionic site. For compounds acting at this site, there is a structure AChE activity relationship due to the distance between the bisquaternary nitrogens.[4,11] The AChE inhibition reaches a maximum IC50 value at a 9- to 10-carbon chain length. Berman and co-workers[6] report IC50 values for various phenanthridium

compounds of chain lengths between quaternary nitrogens of 10 carbons (IC50 = 10^{-6}); 6 carbons (IC50 = 10^{-7}); and 3 carbons (IC50 = 10^{-6}). Loomis' earlier work[11] on bisquaternary nitrogen compounds corroborates the 8-10 carbon separation of the nitrogens for optimum AChE inhibition. The maximum AChE inhibition for Loomis' compounds was made by a bisquaternary compound with a 9-carbon chain between nitrogens.

The computational analysis of the interatomic distances between nitrogens for straight chain bisquaternary hydrocarbons resulted in distances of decamethonium, 14.09 Å; octamethonium, 11.53 Å; and hexamethonium, 8.99 Å. Decamethonium acts at the peripheral AChE site. Compound 4 has a bisquaternary nitrogen distance of 12.13 to 12.56 Å. Its IC50 inhibition corresponds to those compounds with structural features that correlate with peripheral AChE site inhibition.

Similarly, 1 exhibits peripheral site inhibition characteristics (IC50, 10^{-6}) for a compound with a bisquaternary nitrogen distance of 8.03 to 10.59 Å.[6,11]

Compound 3 has bisquaternary nitrogen distances of 9.86 to 12.56 Å, which corresponds to a potential for a peripheral anionic site inhibition. However, the corresponding N+-C=O are much larger than the other compounds studied, and this may cause the resultant decrease in AChE inhibition. That is, the pyridinium ring may be geometrically positioned to be sterically hindered to AChE, and because of this steric hindrance, the AChE inhibition is decreased.

The compound structure file internal format and individual files that list the MM2 program-calculated three-dimensional Cartesian atom coordinates corresponding to the minimum energy optimized geometry, are reported in Appendixes A and B, respectively.

4. CONCLUSIONS

In this series, the 3-substituted isomer 2 is the most potent isomer. Compounds 1-3 were designed to have structural features to enhance activity at AChE. The resultant structure-activity relationships for this series of compounds agree with other studies relating AChE inhibition with specific compound geometric functional group attributes for interaction at the AChE catalytic and/or peripheral anionic sites. Compound 2 incorporates functional groupings within its structure that have interatomic distances similar to both pyridostigmine and to those of bisquaternary compounds that cause 2 to be the most active.

The resultant optimized geometries can be used as initial structural conformations for use in future structure-activity relationship and molecular modeling studies.

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APPENDIX A

COMPOUND STRUCTURE FILE INTERNAL FORMAT

This file is the central data structure of MMADS, containing molecular information that is required to execute any MMADS command. To use the EDIT command properly, the user is expected to understand the format of the individual entries in the file (these have been provided as FORTRAN format fields). The data records contained in the structure file are:

Record #1-	The header record for the file.
Column Nos. 1-3 (i3)	The number of atoms contained in the file.
Column Nos. 4-72 (a)	The title of the structure file.
Record #2 on-	The descriptions of the individual atoms.
Column No. 1 (1x)	blank
Column Nos. 2-3 (a)	The atom symbol. Single letter labels must be preceded by a space.
Column Nos. 4-8 (i5)	The atom index.
Column Nos. 9-20 (f12.6)	The x-coordinate.
Column Nos. 21-32 (f12.6)	The y-coordinate.
Column Nos. 33-44 (f12.6)	The z-coordinate.
Column Nos. 45-59 (i5)	The atom type (see below).
Column Nos. 50-79 (6i5)	The bond connectivity.

MMADS uses the atom type to encode information describing the molecular environment of each atom. Various commands utilize this information to distinguish between identical atoms in different molecular environments, thus providing a better representation for the user. The atom types used by MMADS are:

Atom Type	Description
1	sp3 Carbon
2	sp2 Carbon
3	Carbonyl Carbon
4	sp Carbon
5	Hydrogen
6	sp3 Oxygen
7	sp2 Oxygen
8	sp3 Nitrogen
9	sp2 Nitrogen
10	sp Nitrogen
11	Fluorine
12	Chlorine
13	Bromine
14	Iodine
15-18	Sulfur (this is still under development)
19	Silicon
20	unused
21	Alcoholic Hydrogen (O-H)
22	Cyclopropane Hydrogen
23	Amine Hydrogen
24	Carboxyl Hydrogen
25	Phosphorus
26-27	unused
28	Vinyl Alcohol Hydrogen

APPENDIX B

COMPOUND THREE DIMENSIONAL COORDINATES

48COMPOUND 1 1,4-BIS[2-(1-METHYLPYRIDINO)ACETYL]BENZENE

C	1	-0.520440	-0.535150	-0.425360	2	2	6	33	0	0	0
C	2	0.178520	-1.679980	-0.491710	2	1	3	7	0	0	0
C	3	1.520230	-1.651960	-0.531090	2	2	4	8	0	0	0
C	4	2.178030	-0.479710	-0.507270	2	3	5	32	0	0	0
C	5	1.479740	0.666190	-0.447940	2	4	6	9	0	0	0
C	6	0.137330	0.637560	-0.406150	2	5	1	10	0	0	0
H	7	-0.327060	-2.655040	-0.523780	5	2	0	0	0	0	0
H	8	2.071970	-2.605760	-0.585350	5	3	0	0	0	0	0
H	9	1.986850	1.641580	-0.440580	5	5	0	0	0	0	0
H	10	-0.415770	1.590860	-0.357470	5	6	0	0	0	0	0
C	11	-1.983140	-4.616390	2.700630	2	12	16	17	0	0	0
C	12	-1.973340	-4.982730	1.411520	2	11	13	18	0	0	0
C	13	-2.258920	-4.089660	0.452230	2	12	14	19	0	0	0
C	14	-2.557590	-2.809620	0.743830	2	13	15	34	0	0	0
N	15	-2.576310	-2.429290	2.068690	9	14	16	37	0	0	0
C	16	-2.284060	-3.353280	3.031820	2	15	11	20	0	0	0
H	17	-1.747850	-5.353310	3.487920	5	11	0	0	0	0	0
H	18	-1.728030	-6.023990	1.138810	5	12	0	0	0	0	0
H	19	-2.240220	-4.421870	-0.599570	5	13	0	0	0	0	0
H	20	-2.299950	-3.042000	4.090200	5	16	0	0	0	0	0
C	21	4.294330	1.728940	0.649690	2	22	26	31	0	0	0
C	22	4.061850	3.034590	0.417710	2	21	23	27	0	0	0
C	23	3.941690	3.899600	1.418960	2	22	24	28	0	0	0
C	24	3.850510	3.477110	2.690840	2	23	25	29	0	0	0
C	25	4.084900	2.185920	2.962580	2	24	26	30	0	0	0
N	26	4.311670	1.289860	1.956110	9	25	21	38	0	0	0
H	27	4.046480	3.412850	-0.618440	5	22	0	0	0	0	0
H	28	3.651220	4.963790	1.195370	5	23	0	0	0	0	0
H	29	3.668800	4.190810	3.512940	5	24	0	0	0	0	0
H	30	4.099090	1.828480	4.006290	5	25	0	0	0	0	0
C	31	4.527730	0.793510	-0.525440	1	21	32	39	40	0	0
C	32	3.719240	-0.502060	-0.557420	3	31	4	35	0	0	0
C	33	-2.062290	-0.523260	-0.378470	3	1	34	36	0	0	0
C	34	-2.853890	-1.831080	-0.382370	1	33	14	41	42	0	0
O	35	4.325830	-1.547730	-0.652560	7	32	0	0	0	0	0
O	36	-2.679550	0.520310	-0.366570	7	33	0	0	0	0	0
C	37	-2.927970	-1.093560	2.470160	1	15	43	44	45	0	0
C	38	4.594990	-0.079190	2.293820	1	26	46	47	48	0	0
H	39	5.613850	0.542070	-0.521240	5	31	0	0	0	0	0
H	40	4.345030	1.301520	-1.500280	5	31	0	0	0	0	0
H	41	-3.943160	-1.599200	-0.334010	5	34	0	0	0	0	0
H	42	-2.697330	-2.293670	-1.383980	5	34	0	0	0	0	0
H	43	-2.055430	-0.411970	2.349520	5	37	0	0	0	0	0
H	44	-3.794410	-0.705830	1.889000	5	37	0	0	0	0	0
H	45	-3.243170	-1.042350	3.537320	5	37	0	0	0	0	0
H	46	4.920250	-0.194460	3.352920	5	38	0	0	0	0	0
H	47	3.685620	-0.707420	2.156820	5	38	0	0	0	0	0
H	48	5.432210	-0.485620	1.683250	5	38	0	0	0	0	0